In Defense of Alternative Antihypertensive Therapy

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The standard step-care approach to the treatment of patients with mild hypertension, as outlined in reports of the Joint National Committee for the Detection, Evaluation, and Treatment of Hypertension prior to 1988, has served both the hypertensive patient population and the practicing physician well over the past 10 to 20 years. By bringing to the attention of the patient population the advantages of antihypertensive therapy with regard to a reduction in overall mortality, this approach has increased public awareness and encouraged hypertension-screening programs at worksites, community health fairs, and health care facilities. Concurrently, physicians have proceeded to treat hypertensive patients in an organized fashion, with the result that high blood pressure is controlled in virtually all patients who maintain contact with a physician and who are compliant with their antihypertensive regimen. As Dr. Marvin Moser points out in the preceding article, step-care therapy is an effective treatment for patients with mild forms of hypertension.

We differ in our approach to the treatment of hypertensive patients because, in my opinion, the principal argument in favor of step-care therapy is simply the fact that it has been used successfully for many years. The principal components of step-care therapy, diuretics and/or adrenergic receptor blockers, were among the first agents developed for the treatment of hypertension, and we have the greatest experience with them. The question I would pose is Can we do better? Is there reason to believe that newer antihypertensive agents, if evaluated in properly designed clinical trials, would demonstrate greater efficacy in the reduction of cardiovascular morbidity?

At least four factors suggest that vasodilating agents confer an advantage over diuretics or adrenergic blockers (or both) as the initial therapeutic regimen for patients with hypertension. First, most hypertensive patients manifest an increase in systemic vascular resistance, which leads to compensatory changes in cardiovascular performance. These changes include left ventricular hypertrophy and, sometimes, an increase in left ventricular end-diastolic volume with associated abnormalities of diastolic ventricular filling. Diuretics and adrenergic blockers do little to reverse this underlying physiological abnormality. Indeed, many adrenergic blocking agents increase systemic vascular resistance and decrease cardiac output initially, if not chronically. They thus reduce blood pressure through a cardiosuppressive physiological response. In contrast, adrenergic antagonists, angiotensin converting enzyme inhibitors, and calcium channel blockers lower blood pressure by decreasing systemic vascular resistance and improving or maintaining cardiac output. Further, calcium channel blockers improve ventricular diastolic function.

Second, many questions remain regarding the management of hypercholesterolemia in patients with hypertension. The deleterious effects of antihypertensive therapy on plasma lipoprotein levels are not uniformly accepted. It is clear that diuretic agents have no beneficial effect on lipoprotein metabolism. Although Dr. Moser cites a number of clinical trials in which diuretic therapy produced insignificant changes in total cholesterol levels, other investigators have reported significant increases in total cholesterol levels and decreases in the high density lipoprotein fraction of cholesterol in patients treated with thiazide-type diuretics or adrenergic blockers (or both). The adverse effects of these agents have not been investigated adequately. Dramatic changes can occur in serum cholesterol concentrations in individual patients. Patients receiving diuretic therapy must be carefully monitored for this adverse metabolic side effect.

None of the trials cited by Dr. Moser were designed to measure changes in lipoprotein fractions in response to antihypertensive therapy. Patients were not randomized to therapeutic groups based on lipid variables, nor was any uniform effort made to modify dietary practices, physical activity, or other factors that might lead to changes in cholesterol concentrations in cholesterol concentrations. No trial evaluating patients according to

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these parameters is currently underway. In light of the report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, however, even a 10% increase in plasma cholesterol (accepted by most investigators as a result of thiazide diuretic therapy) will have significant implications for the treatment of hypertensive patients. An increase of this magnitude might be sufficient to increase a patient's cholesterol level from an acceptable range to a new level requiring therapy with cholesterol-lowering drugs. The need for such therapy introduces new problems: patient compliance with multidrug regimens, escalation of the true cost of antihypertensive therapy, and diminished quality of life.

The mortality results from the recently reported MAPHY study address this very issue. This trial, involving a comparison of metoprolol and thiazide diuretics used for the primary prevention of cardiovascular and cerebrovascular deaths demonstrated a significantly lower mortality rate in patients treated with a \( \beta \)-adrenergic blocker than in patients who received diuretics. Why was there a significant difference in the death rate between these two groups? The authors of the report suggested a number of possibilities. Among these were statistically significant differences in the serum potassium and serum cholesterol concentrations in the patients receiving diuretics as compared with those receiving metoprolol. This trial suggests that differences exist among antihypertensive agents with regard to their ability to provide primary protection against death from vascular incidents. Again, this trial raises the possibility that simply lowering blood pressure is not enough.

Third, another important consideration is the quality of life aspect of antihypertensive therapy. Not surprisingly, a recent comparison of captopril, \( \alpha \)-methyldopa, and propranolol found the converting enzyme inhibitor to be superior to the centrally acting sympatholytic or nonselective \( \beta \)-adrenergic blocker with regard to quality of life considerations.\(^9\) Certainly, favorable results from ongoing trials involving \( \alpha \)-adrenergic blockers or calcium channel blockers would not surprise most hypertension specialists. It was noteworthy in the captopril trial that the addition of diuretic therapy adversely affected patients regardless of their initial randomization.

This study did not address the question of whether the addition of a second drug (with the implication of more severe illness) contributed to the negative quality of life effects of the diuretic. Changes in cardiac exercise capacity and alterations in muscle function associated with a falling serum potassium concentration could have contributed to this effect. If one considers the number of patients taking diuretics who eventually will require potassium supplementation, agents that reduce serum uric acid, or, with symptomatic gout, nonsteroidal anti-inflammatory drugs, an adverse effect on the quality of life is not so surprising.

Finally, we should consider the question of the real cost of antihypertensive therapy. The true cost of treating patients is not limited to the price of their medication. Rather, cost includes all the expenses associated with their therapy; these include the cost of the increased frequency of blood testing for monitoring adverse metabolic effects, the cost of additional therapies (whether it be potassium supplements, nonsteroidal antiinflammatory drugs, or uric acid- or cholesterol-lowering agents (or both) used to treat the associated metabolic consequences of the initial antihypertensive therapy), and the cost of adverse effects on the quality of life that accrue from the selection of a less expensive antihypertensive drug. The costs of the latter effects are difficult to measure in dollars and cents. When considered in this context, it is not likely, as Dr. Moser asserts, that the use of alternative therapies will, in fact, result in a decreased adherence to the prescribed antihypertensive regimen. Rather, patients will be more likely to follow their therapeutic regimen.

We now have considerable experience with converting enzyme inhibitors, calcium channel antagonists, and \( \alpha \)-adrenergic blockers in the treatment of hypertension. Certainly, some patients with concomitant diseases are not candidates for the initial use of these therapies, but others may benefit. For example, patients with hypertension and diabetes mellitus may benefit from the use of a converting enzyme inhibitor. Patients with coronary artery disease may find the concomitant use of \( \beta \)-adrenergic blockers and calcium channel antagonists salutary. But for the majority of patients with otherwise uncomplicated mild hypertension, the use of vasodilator therapy permits rapid control of blood pressure 1) in the absence of significant adverse metabolic side effects, 2) without adverse effects on the quality of life, and 3) with an overall true therapeutic cost as low as, if not lower than, that of traditional therapy. Indeed, the most recently published report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recognizes the benefits of alternative therapy.\(^10\) The Committee suggests that angiotensin converting enzyme inhibitors and calcium channel blockers as well as diuretics and \( \beta \)-adrenergic blockers are acceptable initial therapies for patients with mild hypertension.

Until large clinical trials comparing these new alternative therapies with the traditional step-care approach are completed, it is unlikely that this debate will be resolved to everyone's satisfaction. Physicians reasonably may differ in their interpretation of the data currently available. Dr. Moser and I share the goal of improving the health of the untold millions of patients in this country and around the world who have elevated blood pressure. We differ in our interpretation of the available
data and in our use of newly available agents. In response to the challenge Can we do better? My answer is a resounding Yes, through the use of alternatives to traditional antihypertensive therapy.

References


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